Remarks

To expedite prosecution, Applicants have amended claim 31 as suggested by the Examiner to direct it to a specific combination of compounds without reference to therapeutically effective amount. In view of the above, no new matter has been introduced by the amendment and its entry is respectfully requested.

The Examiner rejected claim 31 as allegedly not complying with 35 U.S.C. §112, second paragraph definiteness requirement. While Applicants respectfully disagree, Applicants have amended claim 31 as suggested by the Examiner. Accordingly, Applicants respectfully request that the rejection has been obviated and should be withdrawn.

The Examiner rejected claim 31 under 35 U.S.C. 103(a) as allegedly being unpatentablc over U.S. Patent Application Publication No. 2002/0098185 to Sims et al. ("Sims"), and further in view of U.S. Patent No. 7,005,523 to Dombroski et al. ("Dombroski"). The Examiner acknowledged that "Sims does not explicitly mention that said combination comprises anakinra and IL-18BP, or that IL-1Ra is anakinra" (page 4, last sentence before the first full par. of the 5/20/09 OA). However, the Examiner appears to argue that because the genus of the combination is disclosed, the specific species is not patentable in stating that "there is no need … to bother with "tens of thousands of possible combinations"… [a]ll that an artisan needs to do is to use any of the known IL-1 antagonists… taught by Dombroski" (page 5, lines 7-12 of the 5/20 OA).

Applicants respectfully disagree for the following reasons.

As stated in MPEP 2144.08 "The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a prima facie case of obviousness. In re Baird, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994).

Sims includes description of the genus "IL-18 antagonists", a genus of combinations of IL-18 antagonist with a large additional genus of compounds. The subgenus claimed in this application is the specific combination of IL-18BP (a subgenus of IL-18 antagonsists) and anakinra (which can be considered as a subgenus of the "compounds IL-18 antagonist can be combined with").

Sims only describes a general combination of IL-18 antagonists, not indicating any specific combinations with IL-18BP. Sims lists numerous possible IL-18 antagonists, including soluble IL-18 receptor [0017], IL-18BP [0018], antagonists derived from IL-18 receptors and IL-18BP [0019], antibodies against IL-18 [0020], antisense molecules against IL-18 [0029], ribozymes against IL-18 mRNA [0036]. Thus, in view of the description in Sims, the term "IL-antagonist" itself includes at minimum tens of possible compounds.

In addition, Sims provides a large number of compounds selected from the ones listed in at least paragraphs [0052], and [0057]-[0058] as possible combination compounds with the IL-18 antagonists. To show the extent of the disclosed combinations in Sims, Applicants have compiled the following list from the above-cited paragraphs in Sims:

> another cytokine or cytokine inhibitor; a compound that inhibits the interaction of other inflammatory cytokines with their receptors; examples of cytokine inhibitors include, for example, IFN gamma, IL-6, IL-8, IL-12, IL-15 and TNF, particularly TNF alpha; Anti-inflamatory cytokines include IL-4, TGF beta, and EGF; compounds that interfere with the binding of RANK and RANK-ligand, such as RANK-ligand inhibitors, or soluble forms of RANK, including RANK:Fc; IL-1 antagonist, such as, a soluble IL-1 receptor type II molecule or an antagonistic antibody to the IL-1 receptor; soluble forms of an IL-17 receptor (such as IL-17R:Fc), IL-12 binding protein, or antibodies against CD30-ligand or against CD4; a TNF inhibitor, preferably TNFR:Fc (ENBREL®); pain medications (analgesics), including but not limited to acetaminophen, codeine, propoxyphene napsylate, oxycodone hydrochloride, hydrocodone bitartrate and tramadol; soluble TNF receptor (ENBREL®), methotrexate, sulfasalazine, gold salts, azathioprine, cyclosporine, antimalarials, oral steroids (e.g., prednisone) or colchicine; non-steroidal anti-inflammatories including but not limited to: salicylic acid (aspirin); ibuprofen; indomethacin; celecoxib; rofecoxib; ketorolac; nambumetone; piroxicam; naproxen; oxaprozin; sulindac; ketoprofen; diclofenac; other COX-1 and/or COX-2 inhibitors, salicylic acid derivatives, propionic acid derivatives, acetic acid derivatives, fumaric acid derivatives, carboxylic acid derivatives, butyric acid derivatives, oxicams, pyrazoles and pyrazolones,

> including newly developed anti-inflammatories; topical steroids, systemic steroids, antagonists of inflammatory cytokines, antibodies against T cell surface proteins, anthralin, coal tar, vitamin D3 and its analogs (including 1,25-dihydroxy vitamin D3 and calcipotriene), topical retinoids, oral retinoids (including but not limited to etretinate, acitretin and isotretinoin), topical salicylic acid, methotrexate, cyclosporine, hydroxyurea and sulfasalazine; minocycline; misoprostol; oral collagen; penicillamine; 6-mercaptopurine; nitrogen mustard; gabapentin; bromocriptine; somatostatin; peptide T; anti-CD4 monoclonal antibody; fumaric acid; polyunsaturated ethyl ester lipids; zinc; and other drugs that can be used to treat psoriasis.

Dombroski does not assist one skilled in the art to define the selection of either a specific IL-18 antagonist or any of the compounds it could be combined with. Dombroski is directed to, among others, novel cycloalkyl-[4-(trifluorophenyl)-oxazol-5-yl]-triazolo-pyridines. In column 15, lines 32-43, Dombroski states the following:

> For the treatment of rheumatoid arthritis, the compounds of the invention may be combined with agents such as TNF-alpha inhibitors such as anti-TNF monoclonal antibodies (such as Remicade, CDP-870 and D.sub.2E.sub.7) and TNF receptor immunoglobulin molecules (such as Enbrel®), IL-1 inhibitors, receptor antagonists or soluble IL-1ra (e.g. Kineret or ICE inhibitors), COX-2 inhibitors (such as celecoxib, rofecoxib, valdecoxib and etoricoxib), metalloprotease inhibitors (preferably MMP-13 selective inhibitors), p2X7 inhibitors, .alpha.2.delta. inhibitors, low dose methotrexate, leflunomide, hydroxychloroquine, d-penicillamine, auranofin or parenteral or oral gold.

Therefore, the allegation that a specific combination of IL-18 with anakinra would be obvious when the prior art lists of combinations clearly point to tens of thousands of combination possibilities of possibilities, cannot be sustained.

The Examiner also alleged that a person of ordinary skill in the art would have been motivated to combine IL-18BP with anakinra "**for disease treatment such as rheumatoid arthritis** as Sims and Dombroski teaches [sic] that both antagonsist of IL-1 such as anakinra

(Kineret) and an antagonist of IL-18 such as IL-18BP can be used for treating disorders such as rheumatoid arthritis, and reasonably would have expected to be able to inhibit IL-1 and IL-18, respectively" (page 4, last sentence of 2nd full par.).

This reasoning is against the teachings in the prior art as already discussed in the previous response. Prior art specifically teaches that anakinra **should not be combined with many of the compounds used to treat arthritis and listed in Dombroski as well as Sims**, Specifically, Exhibit I (submitted with the previous response) states that "**Kineret should not be used** with medicines called Tumor Necrosis Factor (TNF blocking agents) such as ENBREL® (etanercept), Humira™ (adalimumab), or Remicade® (infliximab)."

Therefore, to argue that because medicines target the same disease a skilled artisan would be motivated to combine them and expect them to work is not based on the facts in this instance. In the case of anakinra, a toxic reaction resulted from combining it with several other medicines used to treat rheumatoid arthritis (Exhibit I). Accordingly, without the teachings in the present application, a skilled artisan could not have expected combinations with anakinra to work without further extensive experimentation.

The Examiner also alleged that the specification does not teach that the claimed combination avoids the side effects of IL-18BPor IL-1 monotherapy (page 5, lines 7-12 of the full par.). Applicants respectfully disagree. In paragraphs [0041]-[0051] the specification particularly discusses the mechanisms of monotherapy using IL-1 inhibitors and IL-18 inhibitors alone. In paragraph [0051], the specification states that the combination therapy with IL-1 antagonist and IL-18BP overcomes the disadvantage of using IL-1Ra in treatment of RA.

Thus the Examiner's allegation that a skilled artisan would have come up with the specific combination of IL-18BP and anakinra, based on the cited references alone cannot be sustained.

In view of the foregoing, Applicants respectfully submit that all claims are in condition for allowance. Early and favorable action is requested.

In the event that any additional fees are required, the Commissioner is hereby is authorized to charge our deposit account No. 50-0850. Any overpayments should also be deposited to said account.

Date: November 10, 2009

Respectfully submitted,

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